Navigating Controlled Correspondence in Generic Drug Development: A Comprehensive Overview of Guidelines, Submission Processes, and Review Disciplines

S K Shridar*[1] and K Kathiresan[2]

[1]M. Pharm (IP) Student, Department of Pharmacy, FEAT, Annamalai University, Annamalainagar, Chidambaram-608002, Tamil Nadu, India
[2]Associate Professor, Department of Pharmacy, FEAT, Annamalai University, Annamalainagar, Chidambaram-608002, Tamil Nadu, India

ABSTRACT

Controlled correspondence provides a key means of communication between the Food and Drug Administration (FDA) and the generic pharmaceutical industry. Such a framework enables the industry to seek the agency's input prior to submitting an Abbreviated New Drug Application (ANDA). In March 2024, the FDA revised its guidelines for industry-controlled correspondence pertaining to the development of generic drugs, which outline the procedure for generic drug manufacturers, allied industry, or their representatives to submit controlled correspondence to the FDA seeking information about generic drug development. It also laid down additional guidelines for particular kinds of queries in controlled correspondence.

Keywords: Controlled correspondence**,** FDA, Generic drug development, ANDA

INTRODUCTION

A controlled correspondence is a communication sent to the FDA by or on behalf of a generic drug manufacturer or allied industry seeking information on a particular aspect of the development of generic drug products or specific post-approval submission criteria. The Office of Generic Drugs (OGD) accepts written enquiries, known as "controlled correspondence," from the manufacturers of generic drugs and allied industries. These are requests to obtain information regarding post-approval submission processes or a particular aspect of the development of generic drugs. Timelines for evaluating controlled correspondence were agreed upon by the FDA and industry as part of the Generic Drug User Fee Amendments (GDUFA) reauthorisation.[1]

LEVELS OF CONTROLLED CORRESPONDENCE

Level 1

Generic drug manufacturers or allied industries can submit a correspondence to the agency for seeking information on a specific aspect of the development of generic drug products, referred to as level 1 correspondence. It involves requests

- before to submitting an ANDA
- following a teleconference with product specific instructions if a potential applicant or applicant requests additional FDA comments
- after the publication of a provisional approval following ANDA approval

- following ANDA approval

It also refers to correspondence regarding post-approval filing criteria that are not unique to an ANDA and are not addressed by the Centre for Drug Evaluation and Research's (CDER) post-approval adjustments guidance. Within 60 days of the filing date, the FDA will examine and reply to 90% of correspondence in level 1.[1,2] Shown in Fig.1.

Level 2

Level 2 correspondence entails

- assessment of the clinical content
- requires a Covered Product Authorisation (CPA) and an examination of Bio-Equivalence (BE) procedure for evaluation and development involving clinical trials for an ANDA in which the RLD (Reference Listed Drug) is undergoing an ETASU (Elements to Assure Safe Use) and Risk Evaluation and Mitigation Strategy (REMS)
- requests that, in situations when clinical trials are not utilised for development or evaluation, a CPA obtain adequate amounts of a certain covered product that is subjected to a REMS and ETASU
- asks for analyses of different BE strategies
- needs input from a different office or facility

Within 120 days of the filing date, the FDA will examine and reply to 90% of correspondence in level 2. Shown in Fig.1.[1,2]

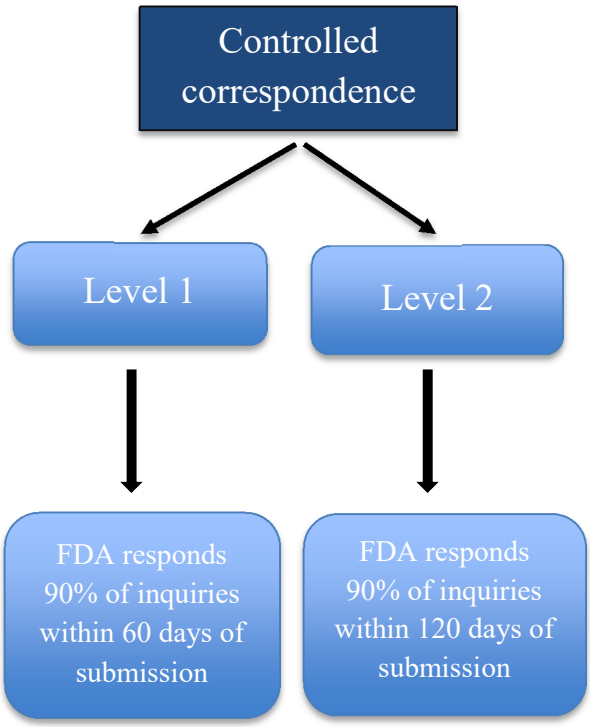

Fig.No:1 Controlled Correspondence Time Line

GUIDELINES FOR INDUSTRY RELATED CONTROLLED CORRESPONDENCE

The Federal Food, Drug, and Cosmetic (FD&C) Act was revised by the GDUFA I 2012, which gave the FDA the authority to evaluate and collect user charges in order to fund the agency's efforts to guarantee that patients have access to high-quality, reasonably priced, safe, and effective generic drugs. Applications for generic drugs are reviewed more quickly and predictably because of GDUFA fee resources. GDUFA has been renewed every five years to maintain the FDA's capacity to evaluate and gather GDUFA fees. This user fee initiative has been renewed twice since GDUFA I, with the latest reauthorisation occurring in the Continuing Appropriations and Ukraine Supplemental Appropriations Act of 2023.[3]

A. Guidance on questions related to controlled correspondence that the FDA is unable to address

1.Controlled correspondence regarding Pending Citizen Petition, Stay of action petition, or petition for Administrative Reconsideration of Action

The FDA intends to reply by stating that we are unable to answer the question because it relates to a petition-related matter and closing the controlled correspondence when one or more pending citizen petitions, stay of action petitions, or requests for administrative reconsideration of action are the subject of a controlled correspondence. The requestor may resubmit the controlled correspondence after the FDA has responded to the pending citizen petition, stay of action petition, or administrative reconsideration of action petition.

2. Requests pertaining to issues the agency is still considering

On occasion, the FDA gets information requests regarding topics it is considering but on which no regulatory or scientific decision has been reached, or on which there isn't a clear consensus among scientists.

B. Guidance on questions not covered by controlled correspondence

Requests for meetings to discuss the generic drug development, reviews of BE research protocols, and the design of BE studies for a particular drug product have been rejected by the FDA.

SUBMITTING A CONTROLLED CORRESPONDENCE

Requesters should use the CDER Direct NextGen Collaboration Portal to electronically send their controlled correspondence in order to receive the FDA's response. According to the evaluation timescales specified in the GDUFA III letter, this procedure will enable the relevant discipline to promptly review and reply to the correspondence. Submitting controlled correspondence to specific FDA workers and sending extra copies of a controlled correspondence via fax, courier, or paper form are severely discouraged by the FDA.[3]

CONTENT OF A CONTROLLED CORRESPONDENCE

The FDA advises that controlled correspondence be sent on business letterhead, dated within seven days of the submission, and contain the following details:

- Name, title, address, phone number, email address, and entity (such as corporate affiliation) of the individual providing the controlled correspondence.
- The FDA advises sending a copy of the CRL (Complete Response Letter) along with a note of any additional controlled correspondence or meeting requests pertaining to the CRL in order to engage in controlled correspondence about it.
- Application number, manufacturer, proprietary name, active ingredient/established name, dosage form, drug administration route, strength, and pertinent RLD and reference standard.
- Declaration that the controlled correspondence pertains to an ANDA that has been approved, received a preliminary approval letter, received a CRL and is pending with the applicant, an ANDA that is pending with the FDA, or a future ANDA submission to OGD.
- A succinct statement outlining the controlled correspondence inquiry and outlining the precise questions that need to be addressed.[3]

REQUESTS FOR INACTIVE INGREDIENTS

A requester may send in

- a request suggesting three inactive substances, each with one level, or
- a request that suggests three levels of one inactive component

A requestor may submit a request if the medication product is recommended for both adult and paediatric populations.

- a request that suggests three distinct dosage ranges for a single inactive ingredient at a single level (based on body weight or age range stated in the RLD labelling), or
- Three inactive substances with a single level for a single dosage range are suggested in this proposal.[3]

REQUESTS FOR FORMULATION ASSESSMENT

According to FDA regulations, proposed products must, for the most part, be qualitatively (Q1) and quantitatively (Q2) identical to the RLD with regard to certain inactive components. Controlled correspondence should have the following details:

- Application recipient
- Application number
- Proprietary or brand name
- The active component
- Indicate the fill volume if the product is a parenteral medication.
- Dosage form
- The administrative route
- Date of approval

- The state of marketing

The FDA strongly discourages sending more than three different formulations of the same drug in a single controlled correspondence.

REQUESTS RELATED TO PRODUCT QUALITY

A succinct explanation of the suggested formulation, manufacturing procedure, container-closure system, and developmental studies should be included in any submission pertaining to product quality.[3]

REQUESTS FOR EVALUATION OF DRUG-DEVICE COMBINATION PRODUCT USER INTERFACE

Comparative assessments, detailed inquiries regarding the proposed generic combination product's user interface, and three samples of each the RLD and the proposed generic combination product should all be included in submissions.[3]

CONTROLLED CORRESPONDENCE REVIEW DISCIPLINES

1. Office of Bioequivalence at OGD

It examines correspondence that includes concerns about the maximum exposure to an inactive substance per day and questions about the preparation of BE research.

2. The Office of Standards and Research at OGD

It examines controlled correspondence sent prior to ANDA submission that includes inquiries concerning complex items, as well as correspondence concerning alternative BE approaches to those suggested in product specific guidance and inquiries concerning the application of modelling and simulation techniques.

3. OGD's Clinical Evaluation and Safety Office

It examines letters that contain inquiries about the user interface of a drug-device combination product that are sent to the Agency following the issue of a CRL or following ANDA approval.

4. The Division of Filing Review, Office of Regulatory Operations at OGD

It examines communication that includes questions about Q1/Q2 sameness as well as questions about the percentage composition of inactive components or the amount per dosage unit.

5. Pharmaceutical Quality Office

Letters with questions about chemistry, production, and controls including product quality microbiological for generic medications are reviewed by the Pharmaceutical Quality Office.

6. Generic Drug Policy Office at OGD

It examines correspondence pertaining to specific reference standard selection queries or RLD designation.

CLARIFICATION OF THE CONTROLLED CORRESPONDENCE RESPONSE

- It is necessary to submit the clarification request within seven days.
- Within 21 days of receiving a request, the FDA will examine and address 90% of requests to address any ambiguities in the controlled response.[2,3]

CONCLUSION

The controlled correspondence for generic drug development guidelines represents a significant advancement in the generic drug industry's cooperation and communication. Stakeholders can use the recommendations to better navigate the regulatory landscape, ask the FDA for advice when needed, and contribute to the availability of high-quality generic medications. If adopted, the concepts of controlled correspondence can result in improved regulatory results and more efficient drug development procedures, which will benefit patients everywhere.

REFERENCES

1. https://www.fda.gov/industry/generic-drug-user-fee-amendments/controlled-correspondence-related-generic-drug-development#submitting_controlled.
2. GDUFA III Commitment letter-https://www.fda.gov/industry/generic-drug-user-fee-amendments/gdufa-iii-reauthorization.
3. Controlled Correspondence related to generic drug development guidance document, march2024-https://www.fda.gov/regulatory-information/search-fda-guidance-documents/controlled-correspondence-related-generic-drug-development.